



ZAP-1 CIP CON

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

6/3/97

Examiner : Paula K. Hutzell

Group Art Unit : 1806

Applicants : Y. Shoenfeld and P. Fishman

Serial No. : 08/487,803

Filed : June 7, 1995

For : IMMUNOTHERAPEUTIC METHOD OF
TREATING CANCEROUS DISEASES BY
ADMINISTRATION OF GAMMA GLOBULINS

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3-3101

Hon. Assistant Commissioner
for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132 OF PNINA FISHMAN

I, PNINA FISHMAN hereby declare and state as follows:

1. I am one of the co-inventors of the subject matter of the above-identified application.

2. I am currently the Head of the Laboratory for Clinical and Tumor Immunology, Felsenstein Research Institute, Rabin Medical Center, Petach Tikva, Israel. I have held this position since 1996. I have been a Professor of Life Sciences at Bar-Ilan University, Israel since 1990..

EXPRESS MAIL
EK708046135US

I received a B.Sc. in Microbiology and Biochemistry in 1970, an M.Sc. in 1983 and Ph.D. in 1987 from Bar-Ilan University, Israel.

I have published over 100 scientific papers in peer-reviewed journals. A copy of my curriculum vitae is attached as Exhibit A.

3. I have read the October 10, 1996 Office Action in the above-identified application and the documents cited therein. I make this declaration to make of record supplemental results which further demonstrate the effectiveness of the methods described in the above-identified application.

4. Specifically, I make this declaration to present the following experimental data generated in my laboratory under my direction and supervision.

Methods:

40 C57BL/6J mice were inoculated with 2.5×10^5 B16-F10 melanoma cells. The mice were treated twice a week by subcutaneous administration of IVIG (whole molecule), F(ab)'₂ or Fc fragments in a concentration of 250 µg/mouse. Each group represented 10 mice. The control group was treated with saline only. After 18 days, the mice were sacrificed, the lungs were taken out, and black melanoma foci were counted under a dissecting microscope.

A true copy of a protocol sheet setting forth details of the experiment is attached as Exhibit B hereto. It is my usual practice to maintain protocol sheets for each experiment conducted in my laboratory.

Results:

The mean number of tumor foci in the control group was 78.2 ± 17.0 . In the IVIG treated group, the mean number of foci was 52.4 ± 15.3 for whole IgG, 47.5 ± 11.2 for $F(ab')_2$, and 52.6 ± 17.9 for Fc. These data indicate that Fc fragments of IVIG are effective in preventing the metastasis of human melanoma in mice.

5. It is my belief that, based on data showing the efficacy of $F(ab')_2$ fragments as disclosed in the application, one can predict with reasonable certainty that Fab or Fab' fragments will exhibit similar properties. This is so because all three types of immunoglobulin fragment bind antigen and lack the Fc portion of the molecule. One of skill in the art knowing the structure of immunoglobulin molecules would recognize that the antigen-binding segment of each type of fragment is the not altered, and that any proposed mechanism of action for $F(ab')_2$ would apply to Fab and Fab' as well.

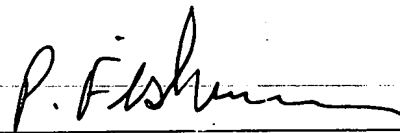
6. Example 2 in the specification describes the effect of IVIG on the development of MCA-105 sarcoma in C57BL/6J mice. In both tumor induction by IV infusion and tumor induction by IP infusion, the results of these experiments show fewer and smaller foci in mice treated with IVIG versus the control (see Figures 5 and 6 respectively). This effect reveals both an inhibition of metastatic foci formation and a negative effect on the growth of the foci once they have been established.

These results relate to the use of IVIG in the treatment of primary tumors in that once established, metastases may be classed with primary tumors by analogy for the purposes of subsequent treatment.

7. Relating to the treatment of Chronic Lymphocytic Leukemia (CLL) with IVIG as described in Besa*, CLL is a unique hematological non-solid tumor which differs in many respects from solid tumors such as carcinoma, melanoma and sarcoma. CLL is an hematological malignancy in which the cancerous cells exist mainly in the blood stream rather than in the tissues. The malignant cells (lymphocytes) are themselves immune cells; 95% of CLL cancer cells are B cells, namely cells producing immunoglobulins and carrying immunoglobulin receptors on their surface, and 5% are T cells. Therefore it is logical that IVIG will work on CLL, because IVIG contains anti-immunoglobulins (e.g. anti-idiotypic antibodies) which bind to the CLL B cells and destroy them. These immunoglobulins do not exist on the cells of solid tumors. CLL is also an immune deficient state (hypogammaglobulinemia); the primary objective of IVIG treatment in Besa was to combat the development of opportunistic infections.

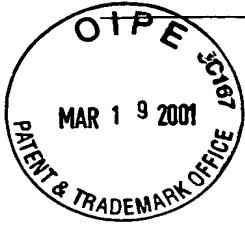
* E. Besa, "Recent Advances in the Treatment of Chronic Lymphocytic Leukemia: Defining the Role of Intravenous Immunoglobulin," Seminars in Hematology, 29, pp. 14-23 (1992).

8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.



PNINA FISHMAN, Ph.D.

Signed this 8 day of
April, 1997
at Herzelya, Israel



Prof. Pnina Fishman, Ph.D.

CURRICULUM VITAE

&

LIST
OF
PUBLICATIONS

January, 1997



CURRICULUM VITAE - SUMMARY

Dr. Pnina Fishman is a professor of Life Sciences at Bar Ilan University, Israel and is heading a Laboratory of Clinical and Tumor Immunology, at the Felsenstein Research Institute, Rabin Medical Center, Israel. She received her Ph.D. from the Bar Ilan University in 1987, has appointed a Senior Lecturer at the Bar Ilan University in 1991 and received her professorship in 1994. Dr. Fishman has published numerous papers in Scientific Journals and has received and filed a number of patents and patent applications.

In 1993 Dr. Fishman, while continuing her academic and scientific work, has established Mor Research Applications (MRA) Ltd., the commercialization arm of applicative research and clinical trials of Kupat Holim Clalit (the largest HMO in Israel which ensures more than 3.5 million people and has under the same management 14 hospitals). Dr. Fishman has served as the General Manager of MRA since its establishment.

Since the establishment of MRA Dr. Fishman was successful in completing numerous technology transfer deals and was involved in the formulation of a number of start-up, development stage companies based on technologies resulting from the R & D activity within Kupat Holim.

In 1994, Dr. Fishman established a division within MRA which operates as a full fledged CRO, providing all around services related to the performance of clinical trials including: study design, clinical monitoring, clinical site and investigator selection, data management, biostatistical studies, bioequivalence studies and preparation of reports for submission to clinical regulatory authorities.

Dr. Fishman managed to negotiate and sign numerous research contracts with Israeli and major international corporations. Dr. Fishman also serves in the Board of Directors of a number of companies.

A detailed C.V. is attached.



CHRONOLOGICAL C.V.

- 1966 - 1970 B.Sc. in Microbiology and Biochemistry. Bar-Ilan University.
- 1970 - 1973 Research in Hematology and Electron Microscopy, Research Institute, Hasharon Hospital, Petach-Tikva.
- 1973 - 1988 In charge of the Electron Microscopy Unit, Hasharon Hospital, which includes Transmission and Scanning electron microscopes and x-ray analytical system.
- 1981 - 1983 M.Sc., Bar-Ilan University. Supervisor: Prof. D. Pluznick. Thesis: Electron microscopy of CFU-C in agar cultures.
- 1984 - 1987 Ph.D., Bar-Ilan University, Department of Life Sciences. Supervisor: Prof. B. Sredni. Thesis: In vitro growth of human basophils and mast cells. Characterization and isolation of their growth factors. Teaching assistant in hematology and immunology.
- 1989 Post Doctoral Research, The effect of AS101 on the production of an anti-tumor factor derived from muscle cultures.
- 1990 Research at Interferon Sciences Inc., a Biotechnology Company in New-Jersey.
- 1991-1995 Head of Research Unit of Clinical Immunology, Research Institute, Hasharon Hospital.
- 1991-1994 Senior Lecturer Bar Ilan University, Dept. of Life Sciences.
- 1993 Establishment of "Mor Research Application Ltd." - the commercialization arm of Applicative Research and Clinical Trials Society Membership of Kupat Cholim.
- 1993-Present General Manager, Mor Research Applications Ltd.
- 1994-Present Professor of life sciences, BAR-ILAN University.
- 1995-Present Head of Research Laboratory of Clinical and Tumor Immunology, the Felsenstein Medical Research Institute, Rabin Medical Center.



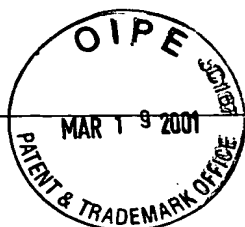
ACADEMIC ACTIVITY

Academic Appointments:

- 1984-1987 Teaching Assistant, Dept. of Life Sciences, Bar-Ilan University. Subjects: Electron Microscopy, Immunology, Cell Biology.
- 1991-1994 Senior Lecturer - Teaching the the courses of Immunophatology, Immunogenetics, Dept. of Life Sciences, Bar-Ilan University.
- 1994-Present Professor of life sciences-Teaching the the courses of Immunophatology, Immunogenetics.

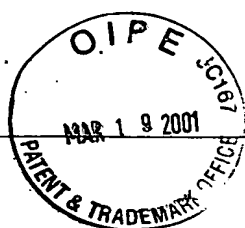
Research Grants and Contracts 1992-1995:

- 1992 Israel Ministry of Health: Spontaneous production of factor with anti-tumor activity by human PBMNC.
- 1992 Israel Ministry of Health: Autoantibodies from patients with Vitiligo are effective against melanoma.
- 1993 Commercial Grant, Biothecnology, Israel: "Why malignant tumors do not metastesize in striated muscles"
- 1994 Tel-Aviv University, The Biology of Cancer Center, Antibodies in melanoma as a diagnostic tool.
- 1995 ARP Biomed Inc. Immunotherapeutic method of treating cancerous diseases by administration of Gama Globulins.
- 1995 Commercial Grant, Purification and characterization of a muscle derived anti-cancerous factor.
- 1995 Commercial Grant, Anti metastatic activity of a blood - derived substance.
- 1996 Israel Ministry of Health: Tyrosinase as an autoantigen in vitiligo - Aplication in melanoma therapy



Research Training of M.Sc. and Ph.D. Students

1987	Shmiel Leonor	Immunological status of uremic patients before and after kidney transplantation.
1988	Shamir Yael	Interleukin-3 levels in women during pregnancy.
1989	Shotlander Varda	Production of interleukin 1,2 and 3 by mononuclear cells from women along the menstrual period.
1989	Nedivi Rannan	Effect of surgery on cytokine production by human mononuclear cells
1990	Falach Emily	Effect of MSS on the functioning of the immunological system.
1991	Hirshfeld Merav	Production of anti-tumor factor by rat muscle cells
1991	Yketzkel Galit	Vitiligo antibodies as immunotherapy for melanoma
1992	Falach Emily	New therapy attitudes for autoimmune diseases
1993	Vagman Limor	Production of anti-tumor factor by human muscle cells
1994	Cohen-Aloro Dina	Purification of a low molecular weight factor with anti-tumoral activity from human mononuclear cells.
1995	Bar Yehuda Sara	Purification and characterization of the muscle factor from a muscle cell line.



Research Training of Medical Students

1972	Avisar Rachamim	Examination of calcium and potassium levels in human saliva for early detection of digoxin intoxication.
1981	Katz Shoshana	The influence of glucose on the phagocytic activity of monocytes
1982	Ishaia Haim	Lithium effect on the granulopoietic system in mice.
1983	Benedek Paul	The effect of long term cholchicine treatment on the protein synthesis and phagocytosis of polymorphonuclears from patients with FMF.
1983	Glazer Tamar	Superoxide anion production by mononuclear cells from uremic patients.
1984	Weinstein Talia	Effect of cimetidine on the growth of bone-marrow CFU-C.
1986	Salman Herzel	Production of interleukin-2 and 3 by peripheral blood cells of cancer patients.
1987	Zeltzer Hela	Production of interleukin-3 by mononuclear cells of patients with Polycytemia Vera.
1987	Diker Dror	Superoxide anion production by neutrophils from patients with myocardial infarction.
1987	Weinstein Talia	Cytokine production by mononuclear cells derived from patients with chronic renal failure and patients on hemo- and peritoneal dialysis.
1988	Djaldetti Ruth	Effect of dexametasone on the production of interleukin-3 by mononuclear cells.
1989	Adler Lili	The level of interleukin 1,2, and 3 in patients after splenectomy.
1989	Zalmanovitch Laslo	Production and level of interleukins in patients with breast cancer.



1991	Sabo Gidon	Interleukin-3: Immunoassay in SLE patients.
1992	Merimski Ofer	Detection of antibodies against melanoma by an ELISA assay and its correlation to disease state.
1993	Dror Diker	Neutrophil function in patients with myocardial infarction.
1995	Kamnitz Joshua	The role of interleukin-3 in the development of anemia in geriatric patients.

Society Memberships

- The American Association of Immunologists
- The Clinical Immunology Society
- The Israeli Association of Immunologists
- The Israeli Association of Hematologists
- The Israeli Association of Alergy and Clinical Immunology
- The European Society of Cancer Research
- American Association of Cancer Research



BUSINESS ACTIVITY

Management and director positions

1993- Establishment of Mor Research Applications, Ltd.

1993-Present General Manager of Mor Research Applications Ltd.

Member of the Board of Directors of GeneMedics

Member of the Board of Directors of Curetech

Member of the Board of Directors of Notox

Patents

1. Isolation of Lymphokines. U.S.A. Patent No. 05984 I-1077. 1992.
2. Immunotherapeutic method of treating cancerous diseases by administration of Gamma Globulins.
Patent Number 5562902, Issue date-10/08/96
3. Anti metastatic factor
Patent Number 5,242,692, issue date-9/07/93
4. Cell Growth Regulator Patent Number 08/531,783 Filling Date: 21.9.95.



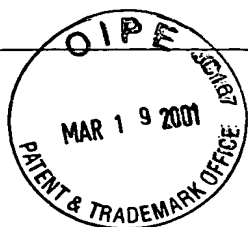
List of Publications

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Active Presentations

in

Scientific Meetings



LIST OF PUBLICATIONS

1. Djaldetti, M., Bessler, H., Fishman, P., Lewinski, U. and Mandel, M.: Ultrastructural features of the white blood cells in the leukemias. Harefuah, 83:528-537, 1972.
2. Bessler, H., Fishman, P. and Djaldetti, M.: Phagocytic activity of Gaucher's cells. Harefuah, 86:173-177, 1974.
3. Djaldetti, M., Bessler, H., Fishman, P., Van der Lyn, E. and Joshua, H.: Ultrastructural features of the granulocytes in Down's syndrome. Scand. J. Haematol., 12:104-111, 1974.
4. Djaldetti, M., Mandel, E.M., Fishman, P., Bessler, H. and Lewinski, U. Intramitochondrial crystalline inclusions in metastatic hypernephroma of the liver. Biomedicine, 21:158-163, 1974.
5. Djaldetti, M., Fishman, P. and Pinkhas, J.: Ultrastructural alterations of the eosinophils in hypereosinophilic syndrome. Harefuah, 88:267-270, 1975.
6. Djaldetti, M., Bessler, H. and Fishman, P.: Hematopoiesis in the embryonic mouse spleen. II. Alterations after phenylhydrazine administration to the mothers. Anatom. Record, 182:123-136, 1975.
7. Djaldetti, M., Ovadia, J., Bessler, H., Fishman, P., and Halbrech, I. Ultrastructural study of the erythropoietic events in human embryonic livers. Biol. Neonate, 26:367-374, 1975.
8. Djaldetti, M., Notti, I., Fishman, P. and Bessler, H.: Transfer of iron-dextran across the placenta. Acta Haematol., 53:292-299, 1975.
9. Djaldetti, M., Elion, D., Bessler, H. and Fishman, P.: Paroxysmal cold-hemoglobinuria. Transmission and scanning electron microscopy features of erythrocytes. Am. J. Clin. Pathol. 63:804-810, 1975.
10. Djaldetti, M., Fishman, P., Bessler, H. and Van der Lyn, E.: Corticosteroid effect on eosinophils in vitro: Ultrastructural studies. Haematologia, 9:65-72, 1975.
11. Djaldetti, M., Bessler, H., Fishman, P. and Mactey, I.: Functional and ultrastructural studies of Sezary cells. Nouv. Rev. Fr. Hematol., 15: 567-574, 1975.
12. Agam, G., Gasner, S., Bessler, H., Fishman, P. and Djaldetti, M.: Chloramphenicol-induced inhibition of platelet protein synthesis: in vitro and in vivo studies. Brit. Jour. Haematol., 33:53-59, 1976.
13. Djaldetti, M., Bessler, H., Mandel, E.M., Weiss, S., Har-Zahav, L. and Fishman, P. Clinical and ultrastructural observations in primary acquired sideroblastic anemia. Nouv. Rev. Fr. Hematol., 15:637-648, 1975.
14. Mandel, E.M., Fishman, P., Kissin, E., Har-Zaav, L. and Djaldetti, M.: Intramitochondrial crystalline inclusions in the liver of a patient with hyperthyroidism. Acta Hepato-Gastroenterol., 23:182-, 1976.

15. Bessler H., Nothi, I., Fishman, P. and Djaldetti, M.: Erythropoietic events in cultured embryonic mouse spleen. *Blood*, 48:419-424, 1976.
16. Djaldetti, M., Bessler, H., Fishman, P., and Apostolov, K.: Erythroid precursor fusion induced by Sendai virus. *Exp. Hematol.* 5:27-40, 1977.
17. Fishman, P., Skutelski, E. and Djaldetti, M.: Ferritin phagocytosis. *Arch. Path. Lab. Med.*, 101:100-102, 1977.
18. Korczyn, A.D., Fishman, P., Djaldetti, M. and Berginer, V.M.: Scanning electron microscope study of erythrocytes from patients with myopathy. *Isr. J. Med. Sci.* 13:131-133, 1977.
19. Djaldetti, M., Gafter, U. and Fishman, P.: Ultrastructural observations in myopathy complicating Cushing's disease. *Am. J. Med. Sci.*, 273:273-277, 1977.
20. Agam, G., Van der Lyn, E., Fishman, P., Bessler, H., Noti, I. and Djaldetti, M.: Effect of cyclophosphamide on metabolic parameters of human platelets and polymorphonuclears. *J. Reticuloendot. Soc.*, 21: 237-244, 1977.
21. Djaldetti, M. and Fishman, P.: Scanning and transmission electron microscopy study on the plasma cells of a patient with multiple myeloma. *Acta Haematol.* 58:173-180, 1977.
22. Lustig, S., Ascher, O., Fishman, P., Djaldetti, M. and Pluznik, D.H.: Correlation between movement concanavalin A membrane receptors and cytolysis. A scanning electron microscopy study. *J. Cell Biol.* 75: 388-397, 1977.
23. Djaldetti, M., Fishman, P., Bessler, H. and Apostolov, K.: SEM observations on Sendai virus - induced fusion of embryonic mouse erythroblasts. *Exp. Hematol.* 6: 321-326, 1978.
24. Djaldetti, M., Goodman, J. A. and Fishman, P.: Ultrastructure of the cells in the peripheral blood of human embryos at early gestational stages. *Biol. Neonate*. 33:177-183, 1978.
25. Djaldetti, M. and Fishman, P.: Satellitism of platelets to monocytes in a patient with hypogammaglobulinemia. *Scan. J. Haematol.* 21:305-308, 1978.
26. Djaldetti, M., Bessler, H. and Fishman, P.: Drug-induced platelet surface alterations. A possible mechanism for impaired aggregation. *Hematologica*, 63:531-547, 1978.
27. Djaldetti, M., Fishman, P. and Bessler, H.: The surface structure of Gaucher cells. *Am. J. Clin. Pathol.* 71:146-150, 1979.
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 36. Djaldetti, M., Fishman, P., Notti, I. and Bessler, H.: The effect of tetracycline administration on iron absorption in mice. *Biomedicine*, 35:150-152, 1981.
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 44. Mittelman, M., Fishman, P. and Djaldetti, M.: Effect of human saliva on the phagocytic activity of polymorphonuclear leukocytes and monocytes. *Biomed. and Pharmacotherapy*, 38:171-175, 1984.

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45. Weinstein, T., Fishman, P., Klein, B., Levi, J. and Djaldetti, M.: Effect of cimetidine on granulocyte-macrophage colony formation by normal and chronic renal failure bone marrow cells. *Kidney Intern.* 26:741-743, 1984.
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 59. Fishman, P., Sredni, B. and Djaldetti, M. Recent advances in interleukin-3 research: A review. *Israel J Med Sci.*, 26(7):414, 1990.

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2. Fishman P., M. Djaldetti, & B. Sredni: Growth of human basophil lines derived from chronic myelocytic leukemia cells in vitro: ultrastructure and X-ray micro-analysis studies. 4th Israel Medical Week - Israel Society of Hematology and Blood Transfusion, 1985.
3. Fishman P., B. Sredni & M. Djaldetti: Characterization of a human factor with Interleukin-3-Like-Activity. Israel Society of Hematology, 1986.
4. Fishman P., H. Salman, B. Sredni & M. Djaldetti: Production of Interleukin-2 and 3 by mononuclear cells of patients with tumors of the gastrointestinal tract. Annual Meeting of the Cancer Biology Research Center of Tel-Aviv University, 1987.
5. Fishman P., R. Djaldetti, B. Sredni & M. Djaldetti: The effect of dexamethasone on IL-3 production by human mononuclear cells. Annual Meeting of the Cancer Biology Research Center, 1988.
6. Fishman P., M. Djaldetti & B. Sredni: Production of Interleukin-3 by mononuclear cells from CML patients: relation to basophil production in vitro. Israel-German Hematology Society, 1988.
7. Djaldetti M., & P. Fishman: Why malignant tumors do not metastasize in striated muscles. Annual Meeting of the Cancer Biology Research Center, 1989.
8. Fishman P., B. Sredni & M. Djaldetti: The effect of dexamethasone on IL-3 production by human mononuclear cells. Second International Symposium on Acute Leukemias, Munster, West Germany, 1989.
9. Fishman P., M. Djaldetti & B. Sredni: Evidence for the presence of a new hematopoietic factor in human synovial fluid. Third Interscience World Conference on Inflammation. Monte-Carlo, 1989.
10. Fishman P., M. Djaldetti & B. Sredni: Spontaneous release of a new hematopoietic factor by human lymphocytes and monocytes. 7th International Congress of Immunology, Berlin, West Germany, 1989.
11. Sredni B., Fishman P., Djaldetti M.: A New human hematopoietic growth factor with basophil promoting activity. 4th interscience conference on inflammation, antirheumatics, analgesics, immunomodulators, Switzerland, 1991.
12. Fishman P., Sredni B., Djaldetti M.: Inhibition of leukemic cell proliferation by a muscle derived factor. 8th Israel Medical Week, MEDAX 91, with 15th World Congress of The Israel Medical Association, Jerusalem, 1991.

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13. Fishman P.: Interleukin-3 and autoimmunity. Autoimmunity Day, Sheba Medical Center, 1992.
 14. Fishman P.: muscle derived factor with anti tumor activity. 22th conference of the Israel Immunological Society, Bar Ilan University. 1992.
 15. Fishman P., Nedivi R., Djaldetti M., Sredni B., Kayzer S., Chaimoff C. Kinetics of cortisol, IL-2 and IL-3-LA levels following surgical intervention. Israel Society of Surgery, Jerusalem, 1992.
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 18. Fishman, M. Djaldetti, E. Falach Vaknine, R. Bakimer, B. Sredni and Y. Shoenfeld. Administration of IL-3 to pregnant mice with experimental anti-phospholipid syndrome. Israel Society of Hematology, Daniel Hotel Herzelia, November 1992.
 19. Fishman. Autoantibodies from patients with vitiligo are cytotoxic against melanoma cells. 8th Mimonides Conference, Ein-Gedi, February 1993.
 20. Fishman. Autoimmunity & Cancer-Enemies or Friends? Vitiligo-Melanoma as an example. Autoimmunity Day No. 7-Shiba Medical Center, February 1993.
 21. Fishman. Lessons in Experimental Anti-Phospholipid Syndrome. Autoimmunity section, Medax, Jerusalem, 1993.
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 25. Shoenfeld, P. Fishman. Cytokine, Interleukin-3, Autoimmunity and Pregnancy. 9th Mediterranean Congress of Chemotherapy. Milano, Italy, June. 1994.
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 32. Merimsky, Y. Shoenfeld, E Baharavi, R. Tsigelman, P. Fishman. Autoantibodies to tyrosinase: Crossroad between vitiligo and melanoma. Human Antibodies and Hybridomas, October, 1996.
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